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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,120	01/12/2001	Sarah S. Bacus	MBHB01-033	1979

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,120	BACUS, SARAH S.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-13,16 and 19-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13,16 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/22/03 has been entered.

Amendment Entry

2. Applicant's amendment and response filed 3/13/03 in Paper No. 10 is acknowledged and has been entered. Claims 15, 17, and 18 have been cancelled. Claims 21-23 have been added. Accordingly, claims 2-13, 16, and 19-23 are pending and are under examination.

Rejections Withdrawn

3. The rejections of claims 15, 17, and 18 are now moot in light of Applicant's cancellation of the claims.

4. In light of Applicant's amendment and argument, the rejection of claim 19 under 35 U.S.C. 112, first paragraph, is hereby, withdrawn.

5. In light of Applicant's amendment and argument, the rejection of claims 2-11, 13, 16, and 20 under 35 U.S.C. 102(b) as being inherently anticipated by Slamon et al. (US 5,846,749), is hereby, withdrawn.

6. In light of Applicant's amendment and argument, the rejection of claims 12 and 19 under 35 U.S.C. 103(a) as being unpatentable over Slamon et al. (US 5,846,749), and Slamon in view of McNamara et al. (US 6,007,996), are hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2-13, 16, and 19-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21, in step b), is vague and indefinite because it is unclear as to whether an average optical density of [all] stained target protein per pixel of cellular area in all the stained plurality of cells, is determined, or that an average optical density of stained target protein per pixel of cellular area *for each of the* stained plurality of cells, is determined. It appears that Applicant should intend the latter. Please clarify.

Claim 21, in step c), is vague and indefinite because it is unclear as to whether a calibration curve relating the known quantity of target protein with the average optical density of [all] stained target protein per pixel of cellular area for all the stained plurality of cells, is generated, or that a calibration curve relating each known quantity of target

protein with the average optical density of each stained target protein per pixel of cellular area for each of the stained plurality of cells, is generated. It appears that Applicant should intend the latter. Please clarify.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 2-11, 13, 16, and 19-23 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Slamon et al. (US Patent 5,846,749) in view of Veltri et al. (US Patent 6,463,438).

Slamon et al. disclose a method of determining expression level of target protein in cells from a homogeneous cell population by immunohistochemically staining the cells in order to provide a spectrophotometric signal capable of quantitation by computerized image analysis. Slamon et al. use immunohistochemically stained control cell pellets (standards) with the method to relate the spectrophotometric signal to the quantitative amount of target protein on an individual cell basis. (See column 2, lines 17-28 and line 58, bridging to column 3, line 27). Specifically, Slamon et al. use two or more control cell pellets (cell compositions) each having different amounts of target protein. The control cells express reproducible amounts of the target protein in different levels within a desired range (see column 4, lines 14-35). All values obtained from the

control cell pellets may be normalized based on the values obtained in direct comparison of the values (see column 4, lines 42-44). Slamon et al. disclose staining the cells using detectably-labeled antibodies directed against the target protein, i.e. surface membrane protein receptor, organelle protein, including glycoproteins, etc. (see column 2, lines 29-51). Various labels for immunohistochemical staining include fluorescers and enzymes which produce a product which absorbs light or fluoresces (chromagen) (see column 3, lines 34-54). In the method, Slamon et al. specifically disclose immunohistochemically assaying the sample and control cell pellets at the same time so as to obtain a direct correlation between the amount of protein present in the cells per cell and the optical density signal observed with the immunohistochemical staining. Thereafter, Slamon et al. prepare a calibration curve relating the optical signal observed with the immunohistochemical staining and the amount of target protein present in the pellet cells. Alternatively, Slamon et al. disclose using a standard curve obtained from a plurality of determinations where the curve is determined by at least two or more assay determinations. Assays used include enzyme linked immunosorbent assay (ELISA). The signal obtained from the sample is related to the concentration curve relating signal to concentration, to concentration of the target protein with known amounts of the protein in the control cell pellets (see column 5). Slamon et al. teach application of the method in determining malignant cell expression in an animal, i.e. Her2/neu overexpression (see columns 7-8).

Slamon et al. differ from the instant invention in failing to disclose determining optical density of stained target proteins per pixel of cellular area in plurality of control cell pellets.

Veltri et al. teach immunostaining biomarker protein in cells using biomarker specific antibody to permit analysis of cellular, i.e. nuclear, features. Specifically, Veltri et al. disclose determining optical density of stained target protein per pixel of cell area, i.e. nuclear or cytoplasmic receptor cites, in a population of nucleated cells (see column 5, lines 1-5, and columns 9, line 42 to column 10, line 62).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Veltri in determining optical density of stained target protein per pixel of cell area, into the method of Slamon because Veltri specifically taught that resulting values of such pixel measurement relate specifically to the target proteins specific in selected cell areas; thus, excludes measurement of nonspecific extraneous proteins.

Slamon et al. and Veltri et al. differ from the instant invention in failing to disclose that the calibration curve is linear.

However, calibration data obtained from standards used in calibration procedures all comprise result effective variables, which the prior art references have shown, are obtained using optimization procedures. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of

Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitation recited in instant claim 19 is for any particular purpose or solve any stated problem and the prior art teaches that calibration curves vary according to the standards being analyzed and conditions incorporated thereto, absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the methods disclosed by the prior art to provide a linear calibration curve, by normal optimization procedures.

9. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Slamon et al. (US Patent 5,846,749) in view of Veltri et al. (US Patent 6,463,438) as applied to claims 2-11, 13, 16, and 20-23 above, and in further view of McNamara et al. (US Patent 6,007,996).

Slamon et al. and Veltri et al. have been discussed supra. Slamon et al. and Veltri et al. differ from the instant invention in failing to disclose staining the biological sample with multiplicity of stains upon which image analysis is performed.

McNamara et al. disclose a method of in situ analysis of biological sample by staining the sample with four different immunohistochemical stains and collecting spectral data wherein each spectrum is associated with a target protein, i.e. cytological marker, that is individually detectable. McNamara et al. use optical filters, i.e. filter-based spectral data collection device, so that each signal from each of the multiplicity of stains used to stain the sample is obtained (see column 31, lines 61-67, column 35, lines 27-38, and column 37). The immunohistochemical stain comprises detectably

labeled antibodies, i.e. anti-Her-2/neu antibody (multiple cancers), which bind target proteins, i.e. Her-2/neu, within or on the cells (see column 36, lines 34-42 and columns 40-41). Detectable labels are listed in column 38, lines 36 to column 39, line 40. McNamara et al. specifically disclose immunohistochemically staining control cells (calibration or reference material) which are simultaneously co-stained with the biological sample, obtaining optical density measurements, and comparing results therebetween (see column 38, lines 4-24).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate multiple immunohistochemical staining as taught by McNamara into the cellular samples in the method of Slamon as modified by Veltri, wherein quantitative optical density measurement of target proteins is performed using image analysis because McNamara specifically taught that use of multiple immunohistochemical staining in combination with spectral imaging allows for simultaneous detection of a plurality of distinct components or target proteins present in a cell.

Response to Arguments

10. Applicant's arguments with respect to claims 2-13, 16, 19-23 have been considered but are moot in view of the new grounds of rejection.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~/641

Gailene R. Gabel
Patent Examiner
Art Unit 1641
December 11, 2003